Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Characteristics of HIV-Infected Patients with Venous Thromboembolism and Different $CD4^+$ T Lymphocyte Levels

Yan-Fen Tang[1,2,*]
Yu Wang[1,2,*]
Tian-Jiao Xue[1,2]
Gang Liu[1,2]
Qi Chen[1,2]
Wen Zhao[1,2]
Yan-Yan Liu[1,2]
Rong-Qian Chen[1,2]
Li Chen[1,2]
Jing Liu[1,2]

[1]Department of Respiratory, Beijing Ditan Hospital, Capital Medical University, Beijing, 100015, People's Republic of China; [2]Clinical Key Department of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, 100015, People's Republic of China

*These authors contributed equally to this work

Objective: This study aims to analyze the clinical characteristics of HIV-infected patients complicated with venous thromboembolism (VTE).

Methods: Seventy HIV-infected patients complicated with VTE were enrolled from Beijing Ditan Hospital Capital Medical University from October 2009 to December 2020 and divided into two groups according to $CD4^+$. The clinical data of 70 patients were observed, including general conditions, laboratory indexes, viral load, antiretroviral therapy (ART) before the diagnosis of VTE, and thrombus treatment.

Results: The patients were divided into two groups according to the $CD4^+$ T lymphocyte count. There were 27 patients with a $CD4^+$ T lymphocyte count ≥200 cells/ul, classified as group A (27/70, 38.6%), and there were 43 patients with a $CD4^+$ T lymphocyte count <200 cells/ul, classified as group B (43/70, 61.4%). In group B, these patients included 37 males and 6 females. The average age was 47.1±12.1 years old. The average levels of the following indexes were: D-dimer, 3.5 mg/L (0.7, 6.9); total cholesterol, 4.4 mmol/L (3.3, 5.5); triglycerides, 1.4 mmol/L (0.9, 2.0); low density lipoprotein, 1.9 mmol/L (1.5,2.5); albumin, 31.8±6.4 g/L; CD4+, 66 cells/ul (18, 127); viral load, 12347 copies/mL (27, 203936). Sixty-three patients (63/70, 90%) had started highly active ART (HAART) before VTE was diagnosed, 37 patients (37/70, 52.9%) were complicated with bacterial pneumonia, 16 patients had *Mycobacterium tuberculosis* (16/70, 22.9%), 13 patients had *Pneumocystis carinii* pneumonia (PCP) (13/70, 18.6%), and eight patients were complicated with cytomegalovirus (CMV) infection (8/70, 11.4%). Twenty-four patients had tumors, and 15 patients had HIV-related tumors (15/70, 21.4%). There were significant differences between the two groups in the time from the diagnosis of HIV to the discovery of thrombosis, the time from ART to the discovery of thrombosis and bacterial pneumonia, and the differences in WBC, PLT, Hb, CRP, PTA, INR, TCHO, LDL-C, ALB, and viral load were statistically significant.

Conclusion: The prevalence of VTE in HIV-infected people in the last 11 years was 1.4%. In patients with a high viral load, CRP, D-dimer levels, and low $CD4^+$ and albumin levels, 11.4–22.9% were complicated with an opportunistic infection, and 21.4% had HIV-related tumors. There were significant differences between the two groups in high viral load, CRP, D-dimer, and low albumin.

Keywords: HIV-infected persons, venous thromboembolism, $CD4^+$ T lymphocytes, disease characteristics

Correspondence: Yan-Fen Tang
Department of Respiratory, Beijing Ditan Hospital, Capital Medical University, No. 8, Jingshun Dongjie, Chaoyang District, Beijing, 100015, People's Republic of China
Tel +86 10 84322963
Fax +86 10 84322146
Email yanfenttang@163.com

Introduction

The clinical and economic burden of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is immense. In the United States, the average incidence rate of VTE is 123/10,000 persons per year,

Received: 25 October 2021
Accepted: 23 December 2021
Published: 28 January 2022

and it is 131/100,000 persons per year in Europe.[1] VTE is a complex multifactorial disease, influenced by acquired or inherited predispositions to thrombosis (eg, thrombophilia), environmental exposures (eg, clinical risk factors), and the interaction between them. The triad includes changes in the constituency of blood (hypercoagulability), changes in the vessel wall (injury), and changes in the pattern of blood flow (venous stasis). The causes for VTE are multifactorial and are not readily apparent in many cases. These physiologic changes can occur as a result of pathology, therapies, and treatments. The following are considered strong risk factors that may predispose someone to VTE: Venous stasis; Hypercoagulable states; Immobilization; Surgery and trauma; Pregnancy; Oral contraceptives and estrogen replacement; and Malignancy.

With the development of modern antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection is increasingly regarded as a controllable chronic disease.[2] Highly active ART (HAART) has successfully extended the life expectancy of HIV-infected patients.[3,4] The incidence rate of acquired immunodeficiency syndrome (AIDS)-related diseases will escalate with the increase of survival rate; in particular, cardiovascular disease is a significant cause of morbidity and mortality in HIV-infected people.[5] Thrombosis may also affect the circulation of superficial veins in the leg and other areas, such as the arm, cerebral, portal, hepatic, renal, and mesenteric veins. The incidence rate of VTE in HIV-infected patients is higher compared with the general population; the risk is increased by 2 to 10 times.[6] HIV infection has been considered a prethrombotic condition. Several studies have reported that the incidence of VTE in HIV-infected people is 0.19–7.63%/year.[6–12] When AIDS patients have unexplained dyspnea or hypoxemia, PE should be included in the differential diagnosis.

In people living with HIV, protein C and S deficiencies, raised circulating pro-inflammatory markers, and endothelial dysfunction are risk factors for VTE. Significant levels of inflammatory and coagulation markers such as increases in CPR and D-dimer. Furthermore, treatment with protease inhibitors and opportunistic infections are postulated to confer an increased risk. Patients on ART live longer, increasing the pool of individuals at risk for VTE. Many studies confirmed that patients with low $CD4^+$ T lymphocyte counts had a higher incidence of venous thrombosis. Viral load is another indicator of a high disease burden of HIV infection. The risk of venous thromboembolism (VTE) in patients living with HIV (PLHIV) is increased in patients who are antiretroviral therapy (ART)-naïve, those with a low cluster differentiation (CD4) counts and virally unsuppressed.

Subjects and Methods

Subjects: The inpatient medical records of Beijing Ditan Hospital Capital Medical University from October 2009 to December 2020 were retrospectively searched. It was found that 5010 people were hospitalized due to HIV infection, and 70 patients were confirmed to have VTE. The prevalence of VTE in hospitalized patients in Beijing Ditan Hospital Capital Medical University alone in the past 11 years was 1.4%. The diagnosis of DVT was determined based on the written report of ultrasonic Doppler examination, and computed tomography pulmonary angiography (CTPA) was performed to determine whether the patients had a PE. The standard definition of HIV infection is HIV confirmed by enzyme-linked immunosorbent assay (ELISA) and Western blot. The AIDS diagnosis met the China AIDS Diagnosis and Treatment Guidelines (2018 Edition) in the diagnosis of AIDS. The patients were divided into two groups according to the $CD4^+$ T lymphocyte count. There were 27 patients with a $CD4^+$ T lymphocyte count ≥200 cells/ul, classified as group A (27/70, 38.6%), and there were 43 patients with a $CD4^+$ T lymphocyte count <200 cells/ul, classified as group B (43/70, 61.4%).

Observation indexes: Demographic information such as gender, smoking, underlying diseases (hypertension, diabetes, coronary heart disease), HIV-RNA viral load, coagulation parameters, blood lipids, serum albumin, homocysteine levels, and opportunistic infection such as *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV), and *Mycobacterium tuberculosis* (MTB), were obtained through consulting case records, and HIV related malignancies, anticoagulant therapy, and whether HAART was started before the diagnosis of VTE, were understood. The risk factors of thromboembolism were evaluated, including immobilization, catheter placement, smoking history, and medication history, especially HAART (including protease inhibitors). The detailed methods were detecting HIV-RNA viral load by the PCR-fluorescence probe method (Roche Diagnostics Ltd, Burgess Hill, UK), CD3/CD8/CD45/CD4 by Flow cytometry, Homocysteine by the Cyclic Enzymatic method (Beijing Jiuqiang Biotechnologies, Inc. China), CRP by the Turbidimetric method (DiaSys Diagnostics Systems GmbH, Germany), Serum albumin by the Bromocresol

Green method (Beijing Leadman Biochemistry Co., Ltd, China), Total cholesterol by the Cholesterol Oxidase method (Beijing Leadman Biochemistry Co., Ltd, China), Triglyceride by the GPO-POD enzymatic method (Beijing Leadman Biochemistry Co., Ltd, China), Low-density lipoprotein by Surfactant Removal method (Sekisui Chemical Co., Ltd, Japan), Blood routine (white blood cell, Flow cytometry; Hemoglobin, colorimetric method), and coagulation markers (FIB, CLAUSS calculation method; others including APTT, D-dimer, etc., Immunoturbidimetric method). The kits for coagulation markers were APTT (HemosIL SynthASII 0020006800), D-Dimer (HemosIL D-Dimer HS 500,0020500100), FIB (HemosIL Fibrinogen C,0020301100), FDP (HemosIL FDP, 0020009900), PT (HemosIL RecombiPlas Tin 2G,0020003050), and TT (HemosIL Thrombin Time, 0009758515).

Statistical methods: Statistical analysis was conducted using statistical software SPSS 19.0. The Kolmogorov–Smirnov test was used to test whether the continuous variables were normally distributed. Normally distributed continuous measurement data were expressed as mean ± standard deviation (X ± SD) and comparison of two groups used an independent sample *t*-test in case of homogeneity of variance. Count data were expressed as frequency or percentage (%) and compared between groups using the chi-square test. Non-normally distributed continuous measurement data were expressed as M (P25, P75), and the median of continuous variables was compared between groups using the Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant.

Results

Age: There were a total of 70 patients in this study, including 61 males and nine females, and the male to female ratio was 61:9. In group A, the male to female ratio was 24:3, and in group B the male to female ratio was 37:6. The age range of these patients was 20–83 years old, with an average age of 47.8 ± 13.1. In group A, the age range was 21–69 years old, with an average age of 48.9 ± 14.6. In group B, the age range was 20–83 years old, with an average age of 47.1 ± 12.1. There were no significant differences in gender and age between the two groups.

Smoking: There were 21 patients with a smoking history, including nine patients in group A and 12 patients in group B, and the smoking index was 0 cigarette/year (0–118). The difference between the two groups was not statistically significant.

The difference of time on diagnosis and ART with a VTE incidence in HIV patients: The median time from diagnosis of HIV infection to detection of thrombosis was four months (1–60), and there was a significant difference between the two groups. Some patients had started ART before thrombosis was found, and the median time from ART to detection of thrombosis was one month (0–36), and there was a significant difference between the two groups.

Thromboembolic site: Of 70 patients with DVT, 70 had VTE, and 5 had VTE with PE. There were 27 patients with VTE in group A, and three had VTE with PE. There were 43 patients with VTE in group B, and two had VTE with PE.

Combined tumor types: In this study, of the 70 patients with VTE, 24 patients (24/70, 34.3%) were complicated with tumors, where 15 had HIV-related tumors (15/70, 21.4%), including 12 patients with lymphoma (seven patients with Burkitt's lymphoma, four patients with diffuse large B-cell lymphoma, one patient with B-cell non-Hodgkin's lymphoma) and three patients with Kaposi's sarcoma (KS) (two patients with KS of the skin and one patient with disseminated KS).There were 24 patients with tumors in the two groups, 12 patients in each group. Two patients had primary lung cancer; one had primary liver cancer with intrapulmonary metastasis, one had a mediastinal tumor, five had gastrointestinal tumors (one had rectal cancer, two had gastric cancer, and two had colon cancer). Six patients underwent surgical treatment, four of them were treated with sequential chemotherapy after the operation, 15 patients were treated with chemotherapy without surgery, and three patients were not treated with surgery, chemotherapy, or radiotherapy.

Immobilization and aggressive operation: There were 25 patients with immobilization for different reasons when thrombotic events occurred, with eight in group A and 17 in group B. Aggressive procedures (including deep vein catheterization and PICC catheterization) were performed in a total of 20 patients, including 5 in group A and 15 in group B.

Laboratory tests: In the 70 patients, C-reactive protein (CRP) was 32.8 mg/l (4.5–101.9), D-dimer was 2.8 mg/l (0.6–6.8), where D-dimer was >2.75 mg/l in 26 patients (26/49, 53.1%). The mean values of CRP and D-dimer were higher than normal levels. Prothrombin activity (PTA) was 85.8 (20.1%), fibrinogen was 352.0 ± 150.3

mg/dl, international normalized ratio (INR) was 1.1 (1.0–1.2), the viral load was 0–52,453 copies/mL, with a median of 430 copies/mL, which was <20 copies/mL (18/53, 34%) in 18 patients and >10,000 copies/mL (21/53, 39.6%) in 21 patients. In group A, CRP was increased in 16 patients (16/25, 64%), PTA was decreased in one patient (1/27, 3.7%), total cholesterol (TC) was increased in four patients (4/25, 16%), triglycerides were increased in 16 patients (16/25, 64%), low-density lipoprotein cholesterol (LDL-C) was increased in five patients (2/25, 20%), serum albumin was decreased in 17 patients (17/26, 65.4%), and homocysteine was increased in eight patients (8/16, 50%). In group B, CRP was increased in 36 patients (36/41, 87.8%), PTA was decreased in 13 patients (13/42, 31%), TC was increased in one patient (1/40, 2.5%), triglycerides were increased in 18 patients (18/40, 45%), LDL-C was increased in two patients (2/39, 5.1%), serum albumin was decreased in 40 patients (40/43, 93%), and homocysteine was increased in 10 patients (10/29, 34.5%). In this study, CRP and D-dimer levels were increased, and there was a significant difference between the two groups. The average value of D-dimer was 2.8 mg/l, and its average value in group B was as high as 3.5 mg/l, but there was no significant difference between the two groups.The median number of $CD4^+$ T lymphocytes was 130 cells/μL, $CD4^+$ T lymphocyte count was <200 cells/μL in 43 patients (43/70, 61.4%), including <100 cells/μL in 28 patients (28/70, 40%); the viral load was 0–52,453 copies/mL, with a median of 430 copies/mL, including >10,000 copies/mL in 21 patients.

HAART when VTE was diagnosed: Sixty-three patients (63/70, 90%) had started HAART when VTE was diagnosed. There were 25 patients in group A (25/70, 35.7%), and the treatment of two patients was unknown, while of the 38 patients (38/70, 54.3%) in group B, four patients did not undergo HAART, and the treatment of one patient was unknown. Fifteen patients (15/24, 62.5%) had started ART when the tumor was detected, and the remaining nine patients did not receive ART. The time from the diagnosis of a tumor to the diagnosis of HIV was 1–108 months, with an average of 36 months. In this study, six patients were treated with lopinavir (LPV), including one patient in group A and five patients in group B.

Treatment regimen of DVT: Of the 70 patients, 18 (18/70, 25.7%) were not treated with anticoagulant therapy, and the other 52 patients were treated with related therapy. In group A, thrombolysis combined with low-molecular-weight heparin anticoagulation was performed in one patient, filter implantation combined with low-molecular-weight heparin anticoagulation was performed in one patient, low-molecular-weight heparin anticoagulation was performed in 19 patients, and six patients were not treated with anticoagulation. In group B, 31 patients did not receive anticoagulation with low-molecular-weight heparin treatment, and 12 patients were not treated with anticoagulation.

Complications: Thirty-seven patients had bacterial pneumonia (37/70, 52.9%), 16 had TB infection (16/70, 22.9%), 13 had pneumospore pneumonia (13/70, 18.6%), and eight patients had CMV infection (8/70, 11.4%). In group A, 10 patients had bacterial pneumonia (10/70, 14.3%), four had TB infection (4/70, 5.7%), two had PCP (2/70, 2.9%), and one patient had CMV (1/70, 1.4%). In group B, 27 patients had bacterial pneumonia (27/70, 38.6%), 12 had TB infection (12/70, 17.1%), 11 had PCP (11/70, 15.7%), and seven patients had CMV (7/70, 10%).

Comparison of clinical characteristics of two groups of patients: The data of group A (n = 27) and group B (n = 43) were compared, and there were no significant differences in gender, age, smoking index, TB infection, PCP, CMV, homocysteine, triglycerides, D-dimers, fibrinogen, immobilization, and aggressive operations between the two groups ($P > 0.05$). However, there were significant differences in the time from the diagnosis of HIV infection to the detection of thrombosis, the time from the beginning of ART to the detection of thrombosis, combined with bacterial pneumonia, leukocytes, hemoglobin, platelets, CRP, PTA, INR, total cholesterol, low-density lipoprotein, albumin, and viral load ($P < 0.05$, Tables 1 and 2).

Discussion

Some specific factors in the population of HIV patients are considered to be related to the occurrence of VTE.[13] Many studies reported that the median age of occurrence of VTE in HIV-infected patients was 40 years old, which was 20 years younger than uninfected patients. The annual incidence of VTE in HIV-infected persons younger than 50 years old was significantly higher than in older healthy controls.[14] A hypercoagulable state is considered the state in which the increase of procoagulant components or the decrease of anticoagulant factors makes the blood system prone to thromboembolism. Because of residual chronic inflammation and chronic immune activation, the hypercoagulable state of HIV patients may be affected by

Table 1 Comparison of General Situations Between Two Groups

	Sum (n=70)	Group A(n=27)	Group B (n=43)	t	P
Gender (Male:Female)	61:9	24:3	37:6	X^2=0.120	0.729
Age (Years old)	47.8±13.1	48.9±14.6	47.1±12.1	t =0.123	0.597
Smoking index (cigarette/year)	0(0, 118)	0(0, 200)	0(0, 90)	Z=−0.022	0.982
Time from diagnosis of HIV to detection of thrombosis (m)	4 (1, 60)	24 (3, 72)	2 (1, 24)	Z=−2.030	0.042
Time from diagnosis of HIV to antiviral treatment (m)	1(1, 2)	1(1, 1)	1(1, 3)	Z=−0.936	0.349
Time from antiviral therapy to occurrence of thrombosis (m)	1(0, 36)	36(1, 60)	1 (0, 2)	Z=−3.134	0.002
Immobilization (n)	25	8	17	χ^2=0.709	0.400
Aggressive operation (n)	20	5	15	χ^2=2.177	0.140
Hypertension (n)	14	7	7	χ^2=0.965	0.326
Coronary heart disease (n)	6	4	2	χ^2=2.186	0.139
Diabetes mellitus (n)	8	4	4	χ^2=0.498	0.480
Bacterial pneumonia (n)	37	10	27	χ^2=4.415	0.036
Combined tuberculosis (n)	16	4	12	χ^2=1.612	0.204
Combined PCP(n)	13	2	11	χ^2=3.623	0.057
Combined CMV (n)	8	1	7	χ^2=2.591	0.107

Abbreviations: PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus.

Table 2 Comparison of Laboratory Test Results Between the Two Groups

	Sum (n=70)	Group A (n=27)	Group B (n=43)	t	P
$CD4^+$ T lymphocyte	130 (52, 335)	358 (324, 586)	66 (18, 127)	Z=−7.005	0.000
White blood cell	5.2 (3.9, 7.6)	6.7 (5.0, 9.3)	4.6 (3.5, 7.1)	Z=−2.564	0.010
Red blood cell	3.3±0.9	3.6±0.6	3.2±1.0	t=0.204	0.076
Hemoglobin	106±28.2	118.5±18.5	98.3±30.5	t=0.071	0.003
Hematocrit	31.7±7.9	35.4±5.4	29.4±8.4	t=0.132	0.002
Platelet	183.4±88.4	230.6±90.9	153.8±73.6	t=0.681	0.000
C-reactive protein	32.8 (4.5, 101.9)	11.4 (3.0,47.1)	46.0 (12.8, 124.0)	Z=−2.329	0.020
Prothrombin activity	85.8±20.1	93.1±17.8	81.2±20.3	T=0.365	0.015
Fibrinogen	352.0±150.3	339.9±105.2	359.5±173.3	t =−0.558	0.579
International normalized ratio	1.1 (1.0, 1.2)	1.0 (1.0,1.1)	1.1 (1.0,1.3)	Z=−2.417	0.016
D-dimer	2.8 (0.6,6.8)	1.4 (0.5,6.6)	3.5 (0.7,6.9)	Z=−0.371	0.711
Total cholesterol	3.7 (3.0,4.6)	4.3 (3.1,5.5)	4.4 (3.3,5.5)	Z=−2.528	0.011
Triglyceride	1.7 (0.9,2.5)	2.0 (1.0,2.9)	1.4 (0.9,2.0)	Z=−1.401	0.161
Low density lipoprotein	2.0 (1.6,2.6)	2.2 (1.8,3.4)	1.9 (1.5,2.5)	Z=−2.340	0.019
Albumin	33.2±7.2	35.6±7.9	31.8±6.4	t =0.249	0.031
Homocysteine	12.8 (9.5,19.7)	14.4 (10.3,19.3)	12.1 (9.1,20.3)	Z=−0.952	0.341
Viral load	430 (0,52,453)	0 (0,4063)	12,347 (27,203,936)	Z=−2.817	0.005

various mechanisms. In fact, HIV-infected patients are characterized by significant levels of inflammatory and coagulation markers, such as increases in CPR and D-dimer.[15] Mild to moderate homocysteinemia is common in HIV-infected patients, especially those who undergo combination antiretroviral therapy (cART); the prevalence is 11–29%.[16,17]

Many studies confirmed that patients with low $CD4^+$ T lymphocyte counts had a higher incidence of venous thrombosis.[11,18–20] Several risk factors strongly correlated to VTE, including the diagnosis of AIDS, the deficiency of protein S and protein C, and the low $CD4^+$ cell counts (especially in the presence of clinical AIDS) correlating with the development of VTE.[6] Some studies have confirmed that patients with low $CD4^+$ cell counts are prone to develop venous thrombosis.[11] It has been proposed that there is a correlation between low protein S levels and low $CD4^+$ cell counts,[20] and patients with $CD4^+$ cell counts below 200

cells/μL have a higher prevalence of protein S deficiency compared to patients with $CD4^+$ cell counts above 200 cells/μL.[18] In addition, opportunistic infections are correlated with $CD4^+$ T cell levels, and it has been shown that in HIV patients with clinical evidence of thrombosis and laboratory findings consistent with a hypercoagulable state, common infections include PCP and CMV. Therefore, the production of thrombosis in HIV-infected patients is often associated with the presence of opportunistic infections and also with low $CD4^+$ T-cell levels.[18] HIV patients with VTE presented elevated levels of D-dimer, vWD and total protein S-antigen, and decreased levels of protein C-antigen and free protein S compared to patients without VTE. These abnormal markers are also associated with the degree of immunosuppression detected by $CD4^+$ cell counts.[19] The correlation between $CD4^+$ cell counts and risk of thrombosis may be related to the increased hypercoagulable state found in progressive immunosuppression and HIV disease progression. As the disease progressed, abnormalities in procoagulant and anticoagulant factors worsened the predisposition to thrombosis.

Viral load is another indicator of a high disease burden of HIV infection. Low $CD4^+$ T lymphocyte counts and high viral loads indicate the progression of HIV and usually complement each other in the absence of treatment. In HIV-infected patients, a higher viral load and lower number of $CD4^+$ T lymphocytes are associated with a higher risk of thrombosis.[21,22] Although ART has a certain efficacy, however, patients with HIV infection may still develop an opportunistic infection, depending on their immune status. Concurrent HIV infection and opportunistic infection seem to be risk factors for thrombosis. Thrombotic events are most commonly reported with CMV, PCP, and TB infection. Some case studies have described CMV active infection as a recognized cause of thrombosis.[23–28] In HIV-positive individuals, the incidence of VTE in the presence of CMV was about 9.8%.[29] VTE associated with PCP may be secondary to a hypercoagulable state in patients with AIDS. Because PE and PCP show similar signs and symptoms, PE may not be fully diagnosed.[30,31] Tuberculosis is the most common opportunistic infection in HIV-infected patients, accounting for about 26% of AIDS-related deaths.[32] Patients with MTB infections may have systemic hypercoagulability due to thrombocytosis, anticardiolipin antibody induction, and increased thrombin production. Tuberculosis exacerbated HIV infections, leading to high incidences and high mortality rates.[33] A hypercoagulable state associated with HIV complicated with TB infection is considered a permanent risk factor for VTE. The risk of cancer in HIV-infected persons and AIDS patients is increased.[34] Compared with the general population, the risk of KS is increased by 3640 times, the risk of non-Hodgkin's lymphoma (NHL) is increased by 77 times, and the risk of cervical cancer is increased by six times in HIV-infected persons.[35] The malignant tumor itself is an important high-risk factor for VTE; the interaction between malignant tumor cells and their products and host cells produces a hypercoagulable state, which reduces the body's function of preventing thrombosis. Most patients with malignant tumors have abnormal coagulation mechanisms, such as increased fibrin degradation products (FDP), increased platelets, hyperaggregation of platelets, low fibrinolysis, and hyperplasma fibrinogen. The risk of VTE in tumor patients is increased by at least 4–6 times than in non-tumor patients, resulting in a significant decrease in survival. KS is the most common malignant tumor of VTE in HIV patients. Some relevant summaries reported that the incidence of thromboembolism in HIV-infected patients with KS was 9.3–20%.[12,14,22] The use of HAART, especially protease inhibitor (PI), is associated with thrombotic events.[10,11,36,37] PIs are considered to interfere with liver metabolism, especially cytochrome P450 metabolism and thromboprotein regulation. They can interfere with the reduction of anticoagulant effect in the body or produce endothelial or platelet dysfunction, which eventually leads to the prethrombotic state of HIV-infected patients, thereby increasing the risk of thrombosis.[21] PI can also interfere with the regulation of cholesterol metabolism, resulting in hypercholesterolemia.[38] The treatment of VTE in HIV-infected patients should be the same as that in non-HIV-infected patients, including long-term prevention with low-molecular-weight heparin and warfarin in patients with recurrent thrombosis. In the population of this study, 18 patients did not receive any treatment, 52 patients were anticoagulated with low-molecular-weight heparin in the hospital, and 18 patients continued to use warfarin for anticoagulation after discharge. Because of the increased risk of thromboembolism in HIV/AIDS patients, the life span of HIV-infected patients receiving effective ART will be prolonged. In the future, more HIV-infected patients will receive oral anticoagulants and ART at the same time. The interaction between antiretroviral drugs and other drugs has been widely described.[39] The administration time of warfarin and some antiretroviral drugs should be staggered.

Conclusion

In Beijing Ditan Hospital Capital Medical University, the prevalence of VTE in HIV-infected patients in the last 11 years was 1.4%, the patients had high viral loads, low median

$CD4^+$ T lymphocyte counts, high D-dimer levels, elevated CRP levels, and hypoproteinemia. The median $CD4^+$ T lymphocyte count was 130 cells/μL, the incidence of opportunistic infection was 11.4–22.9%, and 21.4% of the patients were complicated with HIV-related tumors. In case of some factors, such as a high viral load, low median $CD4^+$ T lymphocyte count, high D-dimer level, high CRP level, and hypoproteinemia, when HIV/AIDS patients have unexplained dyspnea or hypoxemia, PE should be included in the differential diagnosis. Because this study was a retrospective study, and the number of cases in this study was small. The results had some limitations, which could not fully reflect the clinical characteristics of HIV-infected patients with VTE. Therefore, a larger sample size case-control study is needed to further answer the problems encountered in clinical practice.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Beijing Ditan Hospital Capital Medical University. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Benjamin EJ, Virani SS, Callaway CW. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492. doi:10.1161/CIR.0000000000000558
2. Ghosn J, Taiwo B, Seedat S, Autran B, Katlama C. HIV. *Lancet*. 2018;392(10148):685–697. doi:10.1016/S0140-6736(18)31311-4
3. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860. doi:10.1056/NEJM199803263381301
4. Murphy EL, Collier AC, Kalish LA, et al. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Ann Intern Med*. 2001;135(1):17–26. doi:10.7326/0003-4819-135-1-200107030-00005
5. Mocroft A, Reiss P, Gasiorowski J, et al. Serious fatal and non fatal non AIDS defining illnesses in Europe. *J Acquir Immune Defic Syndr*. 2010;55(2):262–270. PMid: 20700060. doi:10.1097/QAI.0b013e3181e9be6b
6. Bibas M, Biava G, Antinori A. HIV-associated venous thromboembolism. *Mediterr J Hematol Infect Dis*. 2011;3:e2011030. doi:10.4084/mjhid.2011.030
7. Jenkins RE, Peters BS, Pinching AJ. Thromboembolic disease in AIDS is associated with cytomegalovirus disease. *AIDS*. 1991;5(12):1540–1542. PMid: 1667576. doi:10.1097/00002030-199112000-00025
8. Laing RBS, Brettle RP, Leen CLS. Venous thrombosis in HIV infection. *Int J STD AIDS*. 1996; (2):82–85. PMid: 19244539. doi:10.1258/0956462961917410
9. Howling SJ, Shaw PJ, Miller RF. Acute pulmonary embolism in patients with HIV disease. *Sex Transm Infect*. 1999;75(1):25–29. PMid:10448338 PMCid: 1758180. doi:10.1136/sti.75.1.25
10. George SL, Swindells S, Knudson R, Stapleton JT. Unexplained Thrombosis in HIV-infected Patients Receiving Protease Inhibitors: report of Seven Cases. *Am J Med*. 1999;107(6):624–626. doi:10.1016/S0002-9343(99)00296-X
11. Sullivan PS, Dworkin MS, Jones JL, Hooper WG. Epidemiology of thrombosis in HIV-infected individuals. *AIDS*. 2000;14:321.PMid: 10716509. doi:10.1097/00002030-200002180-00015
12. Saber AA, Aboolian A, LaRaja RD, Baron H, Manna K. HIV/AIDS and the risk of deep vein thrombosis a study of 45 patients with lower extremity involvement. *Am Surg*. 2001;67:645–647. PMid: 11450780.
13. Goldhaber SZ. Risk Factors for Thromboembolism. *JACC*. 2010;29:1–7.PMid: 20620709. doi:10.1016/j.jacc.2010.01.057
14. Jacobson MC, Debuze BJ, Aboulafia DM. Thrombotic complications in patients infected with HIV in the era of Highly active antiretroviral therapy: a case series. *Clin Infect Dis*. 2004;39:1214–1222.PMid: 15486847. doi:10.1086/424664
15. Neuhaus J, Jacobs DR, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis*. 2010;201:1788–1795. doi:10.1086/652749
16. Bernasconi E, Uhr M, Magenta L, Ranno A, Telenti A. Homocysteinemia in HIV-infected patients treated with highly active antiretroviral therapy. *AIDS*. 2001;15:1081–1082.PMid: 11400001. doi:10.1097/00002030-200105250-00027
17. Guaraldi G, Ventura P, Garlassi E, et al. Hyperhomocysteinemia inHIV-infected patients: determinants of variability and correlations with predictors of cardiovascular disease. *HIV Med*. 2009;10:28–34. PMid: 19125962. doi:10.1111/j.1468-1293.2008.00649.x
18. Feffer SE, Fox RL, Orsen MM, Harjai KJ, Glatt AE. Thrombotic tendencies and correlation with clinical status in patients infected with HIV. *South Med J*. 1995;88(11):1126–1130. PMid: 7481983. doi:10.1097/00007611-199511000-00008
19. Klein SK, Slim EJ, de Kruif MD, et al. Is chronic HIV infection associated with venous thrombotic disease? A systematic review. *Neth J Med*. 2005;63:129–136. PMid: 15869040.
20. Karpatkin S, Nardi M, Green D. Platelet and coagulation defects associated with HIV-1-infection. *Thromb Haemost*. 2002;88:389–401. PMid: 12353066. doi:10.1055/s-0037-1613228
21. Saif MW, Bona R, Greenberg B. AIDS and thrombosis: retrospective study of 131 HIV-infected patients. *AIDS Patient Care STDS*. 2001;15(6):311–320. PMid: 11445013. doi:10.1089/108729101750279687
22. Crum-Cianflone NF, Weekes J, Bavaro M. Thromboses among HIV-infected patients during the highly active antiretroviral therapy era. *AIDS Patient Care STDS*. 2008;22(10):771–778. PMid:18783326 PMCid: 2753452. doi:10.1089/apc.2008.0010
23. Lijfering WM, Sprenger HG, Son van WJ. Mesenteric vein thrombosis associated with primary cytomegalovirus infection: a case report. *Blood Coagul Fibrinolysis*. 2007;18:509–511. doi:10.1097/MBC.0b013e3281a3bef9
24. Abgueguen P, Delbos V, Ducancelle A, Jomaa S, Fanello S, Pichard E. Venous thrombosis in immunocompetent patients with acute cytomegalovirus infection: a complication that may be underestimated. *Clin Microbiol Infect*. 2010;16:851–854. PMid: 19686279. doi:10.1111/j.1469-0691.2009.03022.x
25. Tichelaar VY, Sprenger HG, Mäkelburg AB, Niesters BGM, Kluin-Nelemans HC, Lijfering WM. Active cytomegalovirus infection in patients with acute venous thrombosis: a case-control study. *Am J Hematol*. 2011;86(6):510–512. PMid: 21509792. doi:10.1002/ajh.22006

26. Justo D, Finn T, Atzmony L, Guy N, Steinvil A. Thrombosis associated with acute cytomegalovirus infection: a meta-analysis. *Eur J Intern Med*. 2011;22(2):195–199. Epub 2010 Dec 16. doi:10.1016/j.ejim.2010.11.006
27. Atzmony L, Halutz O, Avidor B, et al. Incidence of cytomegalovirus-associated thrombosis and its risk factors: a case-control study. *Thromb Res*. 2010;126(6):e439–43. doi:10.1016/j.thromres.2010.09.006
28. Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV infected adults and adolescents. *MMWR Recomm Rep*. 2009;58(RR–4):1–207. PMCid: 2821196.
29. Mulder R, Tichelaar YI, Sprenger HG, et al. Relationship between cytomegalovirus infection and procoagulant changes in human immunodeficiency virus-infected patients. *Clin Microbiol Infect*. 2011;17(5):747–749. doi:10.1111/j.1469-0691.2010.03415.x
30. Santiago MB, Cossermelli W, Tuma MF, et al. Anticardiolipin antibodies in patients with infectious diseases. *Clin Rheumat*. 1989;8:23–28. doi:10.1007/BF02031064
31. Sule AA, Pandit N, Handa P, et al. Risk of venous thromboembolism in patients infected with HIV: a cohort study. *Int J Angiol*. 2013;22:95–100. doi:10.1055/s-0033-1333866
32. World Health Organization. *Global Tuberculosis Report 2019*. Geneva, Switzerland: World Health Organization; 2019.
33. Tornheim JA, Dooley KE. Tuberculosis associated with HIV infection. *Microbiol Spectr*. 2017;1:5.
34. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer*. 2008;123(1):187–194. PMid: 18435450. doi:10.1002/ijc.23487
35. Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A, McKenna MT. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years-United States, 2008. *MMWR Recomm Rep*. 2008;57(RR–10):1–12.
36. Majluf-Cruz A, Silva-Estrada M, Sánchez-Barboza R, et al. Venous Thrombosis among patients with AIDS. *Clin Appl Thromb Hemost*. 2004;10(1):19–25. PMid: 14979401. doi:10.1177/107602960401000104
37. Lijfering WM, Ten Kate MK, Sprenger HG, Van der Meer J. Absolute risk of venous and arterial thrombosis in HIV-infected patients and effects of combination antiretroviral therapy. *J Thromb Haemost*. 2006;4:1928–1930.PMid: 16961600. doi:10.1111/j.1538-7836.2006.02047.x
38. George SL, Swindells S, Knudson R. Unexplained thrombosis in HIV-infected patients receiving pro- tease inhibitors: report of seven cases. *Am J Med*. 1999;107:624–626. doi:10.1016/S0002-9343(99)00296-X
39. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165:1095–1106.PMid: 15911722. doi:10.1001/archinte.165.10.1095